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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 03/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/802,445	NEST ET AL.	
	Examiner	Art Unit	
	Daniel M Sullivan	1636	

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This Non-Final Office Action is a response to the "Amendment under 37 C.F.R. §1.111" Filed 21 December 2002 (Paper No. 16) in response to the Non-Final Office Action mailed 24 September 2002 (Paper No. 14). Claims 1-22 were considered in Paper No. 14. Claims 1, 5, 9 and 13 were amended and claims 17-22 were canceled in Paper No. 16. Claims 1-16 are pending and under consideration herein.

Response to Amendment

Rejection of claims 17-22 is rendered moot by the cancellation of the claims in Paper No. 16.

Claims 1-16 stand rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement for reasons of record in Paper No. 14 and herein below.

Response to Arguments

This Office Action is made Non-Final in order to clearly set forth the claim rejections as they pertain to claims 1-8, which claims were inadvertently omitted from the second enablement rejection beginning on page 5 of Paper No. 14. In addition, upon further consideration, the Examiner feels that the scope of the enabled subject matter is narrower the scope indicated in the previous office action. Therefore, Applicant's arguments regarding the previous office action are addressed immediately below, and a new enablement rejection is set forth under the heading of ***New Grounds***, in which the subject matter enabled by the disclosure is indicated.

In response to the rejection of claims 1-22 as lacking enablement for reducing the severity of a symptom of papillomavirus infection in any individual or mammal, Applicant cites *Atlas Powder Co. v. Dupont* and argues that the possibility that the invention may not work in every species encompassed by the claim does not necessarily render the claim nonenabled, and cites MPEP 2164.08(b) which states, "[t]he standard [for enablement] is whether a skilled person could determine which embodiment...would be inoperative *with the expenditure of no more effort than is normally required in the art.*" Applicant further argues, "[p]articularly, since the Examiner has conceded that the invention is enabled in *four mammalian species*, a determination of which mammalian species would constitute operative embodiments of the invention as presently claimed would require an expenditure that is no greater than what *is normally* required" (paragraph bridging pages 4 and 5).

This argument has been fully considered but is not found persuasive because it fails to take into account the breadth of the immunostimulatory sequences encompassed by the claim. MPEP 2164.08(b) also provides, "the scope of the claim may still not be enabled where undue experimentation is involved in determining those embodiments *that are operable*" (emphasis added). The claims encompass a method of using an ISS comprising the sequence 5'-C,G, pyrimidine, pyrimidine, C,G-3' in any and all mammals. As pointed out in the previous office action, the art teaches that the operability of any given ISS in one species of mammal is not a predictor of operability in any other mammalian species. Therefore, although determining if any single ISS is operable in a given mammal may not require undue experimentation, determining that the invention would be inoperable in any given mammal would require testing many

thousands of potential immunostimulatory sequences in that mammal. As the art indicates that the vast majority of these sequences would be inoperable in any given species, determining that the invention is inoperable in any given species would require undue experimentation.

Applicant further argues that the claims are enabled over their full scope because the working examples that are provided in the specification are well-accepted model systems for the study of papillomavirus infection in mammals. This argument is not persuasive because, although the working examples are model systems for papillomavirus infection in mammals, the basis of the rejection is the unpredictability ISS efficacy in different mammalian species. The art teaches that success in treating *any* condition using ISS in one mammal is not a predictor of success in treating that same condition in another mammalian species because the determinants of ISS efficacy differ from one species to the next.

Finally, Applicant submits that the degree of experimentation required would not be undue in light of teachings in the specification showing working examples in two mammalian species and teachings from the art indicating enablement in two additional mammalian species. Applicant argues that, armed with these teachings, it would be routine for one of skill in the art to make an ISS according to the claims. These arguments have been fully considered but are not found persuasive. Applicant is arguing that because the specification and prior art teaches methods by which one of skill in the art could evaluate whether a given embodiment of the claimed subject matter would be useful, the claim to a method of treating papillomavirus infection in any mammal is fully enabled. However, *Atlas Powder Co. v. E.I. du Pont de Nemours & Co* (224 USPQ 409, 414; *Id.*) provides, "[o]f course, if the number of inoperative combinations becomes significant, and in effect forces one of ordinary skill in the art to

experiment unduly in order to practice the claimed invention, the claims might indeed be invalid" (page 414). Applicant's arguments fail to take into account the enormous scope of ISS that would have to be evaluated to determine that the method is inoperable in any given species. As the art clearly teaches that an example of an effective ISS in one species provides no guidance with regard to which potential ISS would be effective in another species, determining which embodiments that were conceived, but not yet made, would be inoperative or operative would clearly require expenditure of more effort than is normally required in the art.

Regarding rejection of claims 9-22 as lacking enablement for a method and compositions wherein the composition is administered prior to the development of a lesion or outside of the affected area, Applicant asserts that the Examiner has provided no evidence that a papillomavirus antigen is required in close proximity to the ISS when it is administered, and that, in the present invention, antigen is provided by the active infection at the site of a papillomavirus lesion. Applicant is directed to the following passages in the previous office action:

> With regard to the effectiveness of systemic administration of CpG oligonucleotides and their administration without antigen, the prior art teaches that the effectiveness of immunostimulation with CpG oligonucleotides is dependent on the proximity of the antigen to the site of administration of the oligonucleotide. Weiner et al. (IDS #127) teach that, "Injection of CpG [oligonucleotide] and antigen on the same flank was required for maximal adjuvant effect. Thus, CpG [oligonucleotide] exerts much of its adjuvant effect locally. This finding is consistent with or prior observations that footpad injection with CpG [oligonucleotide] enhances NK activity of cells in the ipsilateral but not contralateral lymph node" (see page 10834, column 1, final paragraph through the first paragraph of column 2 and Figure 4 and the caption thereto). This teaching introduces uncertainty as to whether "an amount sufficient to prevent a symptom of papillomavirus infection" could be achieved in embodiments of the instant invention wherein the CpG oligonucleotide is administered away from the site of antigen. Because the claimed invention is drawn to administration of the CpG oligonucleotide without antigen, antigen is provided by the active infection at the site of the lesion and therefore the teachings of the prior art introduce uncertainty as to whether the invention would be operable when CpG oligonucleotides are administered away from the lesion. (page 6)

> The specification only describes, in specific terms, embodiments of the invention wherein the CpG oligonucleotides are administered by intradermal injection at the site of inoculation with papillomavirus or at the site of a papillomavirus lesion (see especially Examples 1 and 2). The specification further teaches that administration of the CpG oligonucleotides at 1 and 14 days following inoculation with papillomavirus is not effective at reducing the severity of a symptom of papillomavirus infection. (see especially figure 2, panels A and C).

Thus, the previous office action cites teachings from both the prior art and the instant disclosure to support the Examiner's contention that antigen must be present at the time and in the proximity of the administered ISS.

Regarding the Examiner's contention that antigen is provided by the active infection at the site of a papillomavirus lesion, *Ex parte Sudilovsky*, 21 USPQ2d 1702 (BPAI 1991) states, "[t]he *Marzocchi* decision clearly sanctions sound scientific reasoning as an acceptable alternative to patents and printed publications in support of an examiner's holding that a disclosure is not enabling". In the instant case it is reasonable to assume that the antigen is provided by the active infection based on the well established immunological principal that an immune response against any given organism requires antigen. As there is no other source of antigen in the instant case, it stands to reason that the requisite antigen is produced at the site of infection. Applicant is urged to expand the arguments set forth in the present response to indicate why it is not logical to expect that some source of antigen is required for operability of the invention or why it is not reasonable to expect that the infection is the source of the requisite antigen.

New Grounds

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of delaying the development of or reducing severity of a symptom of papillomavirus infection in dogs and rabbits challenged with papillomavirus virus, by administering the *phosphorothioate* polynucleotide comprising the immunostimulatory sequences set forth as SEQ ID NO:1 to said dogs and rabbits at a dose sufficient to prevent, or reduce severity or recurrence of a symptom of herpes infection, does not reasonably provide enablement for a method of reducing the severity of a symptom of papillomavirus infection in any individual or mammal comprising administering any sequence comprising 5'-C,G-3' sequence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

The nature of the invention: The claims are drawn to methods and compositions to be used in the treatment of papillomavirus infection, said methods and compositions comprising ISS sequences.

The breadth of the claims: Given their broadest reasonable interpretation, the claims encompass methods and compositions for treatment of papillomavirus infection in all mammals using any nucleic acid sequence comprising the dinucleotide sequence 5'-C,G-3'.

The state of the prior art and level of predictability in art: The use of CpG sequences as an immunostimulatory adjuvant is well know in the art. However, according to the teachings of Agarwal and Kandimalla (cited in the previous office action), published well after the effective filing date of the instant application, "Although the presence of an unmethylated CpG dinucleotide is essential for the induction of an immunostimulatory activity, the sequences flanking the CpG dinucleotide also play a role", human immune cells respond poorly to the hexameric motif found to be optimal in activating the mouse immune system "suggesting that the sequences required for CpG-related immune stimulation varies from species to species" and "the optimal CpG sequence requirement for many other animal species is not known" (beginning page 114, column 2 final paragraph and continued through the first paragraph of page 115). These comments demonstrate the high degree of uncertainty in the art with regard to extending results obtained using ISS DNAs in one species to other species of mammals. In particular, Hartmann *et al.* (2000) *J. Immunol.* 164:1617-1624 teach that findings obtained using ISS in mice could not be extended to humans. Hartmann *et al.* teach, "[r]ecently, we found that phosphorothioate ODN with the purine-purine-CG-pyrimidine-pyrimidine formula that had been identified as the most stimulatory motif in mice show no or only weak activity in human immune

cells" (final paragraph on page 1617) and conversely, "[t]he human stimulatory ODN...shows weaker activity in mice compared with the highly active murine CpG ODN...supporting the concept of species specificity of CpG DNA recognition by immune cells" (second paragraph on page 1622). Hartmann *et al.* also teach that the effectiveness of any given ISS is unpredictable even within closely related mammalian species. In the second paragraph on page 1622, Hartmann *et al.* teach, "[a]lthough ODN 2006 was active in vitro in all primates tested, other CpG ODN, such as ODN 2007, had relatively high activity in human immune cells but no or a weaker effect in chimpanzees and rhesus monkeys." These teachings demonstrate that the skilled artisan would not be able to use the oligonucleotide sequences or teachings set forth in the specification, which disclose methods and compositions for treating herpes virus infections in dogs and rabbits, to treat herpes virus infection in other mammals, and humans in particular.

Finally, Hartmann *et al.* teaches that use of phosphorothioate backbone, or some other means of protecting the ISS from nuclease degradation is required for *in vivo* clinical utility (first full paragraph on page 1618). Thus, the teachings of the prior art indicate that only the phosphorothioate oligonucleotides taught in the present disclosure would be useful in the methods of the present invention.

The amount of direction provided by the inventor and the existence of working examples: The instant disclosure provides various nucleic acid sequences comprising 5'-CpG-3' and reduction to practice of phosphorothioate oligonucleotides comprising one of those sequences for the treatment of papillomavirus infection in dogs and rabbits. The disclosure does not, however, set forth teachings regarding the requirements unique to the use of CpG oligonucleotides in mammalian species outside of dogs and rabbits.

Relative skill of those in the art: The level of skill in the relevant art is very high. However, because the structural determinants dictating the function of CpG sequences in individual mammalian species are unknown, the prior art does not enable the skilled artisan to extend the explicit teachings found there without significant empirical experimentation.

The amount of experimentation required to practice the invention: Agarwal and Kandimalla (*supra*) teach, "Studies on the medicinal chemistry of CpG DNA have just begun..." and "There is a species-dependent selectivity of CpG DNA, and the optimal CpG DNA sequences for many vertebrate species are not known yet. Medicinal chemistry could help to resolve the issues of species-selective bias of CpG DNA motifs and permit the application of CpG DNA therapeutics for treating veterinary diseases without requiring the identification of optimal sequences for each species" (page 119, column 2, first and second paragraphs of the Concluding Remarks). These remarks show that practicing the claimed invention commensurate with its full scope would require the skilled artisan to identify, through empirical experimentation, an oligonucleotide sequence that can effectively stimulate the immune system of any and all mammals or identify the structural determinants that dictate the species specificity of CpG immunomodulation. This amount of experimentation would place an undue burden on one seeking to practice the invention commensurate with the full scope of the claims.

Thus, due to the art recognized unpredictability of obtaining stimulation of immune responses using CpG oligonucleotides and the lack of guidance in the specification or prior art with regard to how to use the invention in all mammals, it would require undue experimentation to practice the invention commensurate with the full scope of the claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-746-9105 for regular communications and 703-746-9105 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

dms
March 3, 2003

JAMES KETTER
PRIMARY EXAMINER